European Neuropsychopharmacology (2013) 23, 1208–1218

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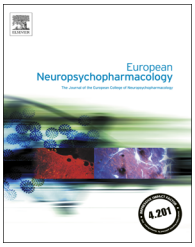

European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder

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Received 27 June 2012; accepted 27 November 2012

KEYWORDS
Adolescent;
Attention deficit disorder with hyperactivity;
Central nervous system stimulants;
Child;
Lisdexamfetamine dimesylate;
Prodrugs

Abstract
This study evaluated the efficacy and safety of lisdexamfetamine dimesylate (LDX) compared with placebo in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) in Europe. Osmotic-release oral system methylphenidate (OROS-MPH) was included as a reference arm. Patients (6–17 years old) with a baseline ADHD Rating Scale version IV (ADHD-RS-IV) total score ≥28 were randomized (1:1:1) to dose-optimized LDX (30, 50, or 70 mg/day), OROS-MPH (18, 36, or 54 mg/day) or placebo for 7 weeks. Primary and key secondary efficacy measures were the investigator-rated ADHD-RS-IV and the Clinical Global Impressions-Improvement (CGI-I) rating, respectively. Safety assessments included treatment-emergent adverse events (TEAEs), electrocardiograms, and vital signs. Of 336 patients randomized, 196 completed the study. The difference between LDX and placebo in least squares mean change in ADHD-RS-IV total score from baseline to endpoint was −18.6 (95% confidence interval [CI]:

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http://dx.doi.org/10.1016/j.euroneuro.2012.11.012

−21.5 to −15.7) ($p<0.001$; effect size, 1.80). The difference between OROS-MPH and placebo in least squares mean change in ADHD-RS-IV total score from baseline to endpoint was −13.0 (95% CI: −15.9 to −10.2) ($p<0.001$; effect size, 1.26). The proportions (95% CI) of patients showing improvement (CGI-I of 1 or 2) at endpoint were 78% (70–86), 14% (8–21), and 61% (51–70) for LDX, placebo, and OROS-MPH. The most common TEAEs for LDX were decreased appetite, headache, and insomnia. Mean changes in vital signs were modest and consistent with the known profile of LDX. LDX was effective and generally well tolerated in children and adolescents with ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders diagnosed in children, with an estimated worldwide prevalence of 5.29% (Polanczyk et al., 2007). ADHD is characterized by persistent core symptoms of hyperactivity, impulsivity, and/or inattention, and is associated with impairments in academic, social, and interpersonal functioning (American Academy of Pediatrics, 2011a; Gordon et al., 2006). Stimulant medications are commonly recommended as part of a comprehensive multimodal treatment plan for ADHD that will often also include behavioral, psychoeducational, and psychological interventions (American Academy of Pediatrics, 2011b; Banaschewski et al., 2006; National Institute for Health and Clinical Excellence, 2009; Taylor et al., 2004). Stimulants are available in long-acting and short-acting formulations. In addition to reducing or eliminating the need for multiple daily dosing, the suggested benefits of long-acting stimulants also include improved adherence and lower abuse potential compared with their short-acting counterparts (Banaschewski et al., 2006).

Lisdexamfetamine dimesylate (LDX) is the first long-acting, prodrug stimulant. The intact parent molecule requires enzymatic hydrolysis to yield the therapeutically-active metabolite *d*-amfetamine (Pennick, 2010). After oral administration, LDX is readily absorbed from the gastrointestinal tract. As the metabolic conversion of LDX to *d*-amfetamine occurs primarily in the blood, it is unlikely to be affected by changes in gastric pH or variations in gastrointestinal transit time (Pennick, 2010). Pharmacokinetic studies in children with ADHD have shown that, following oral administration of LDX, exposure to *d*-amfetamine is long lasting and dose proportional, with low intrapatient and interpatient variability (Biederman et al., 2007a; Boellner et al., 2010).

All clinical trials of LDX reported to date have been conducted in the United States. These studies have shown LDX to be an effective once-daily treatment for ADHD in children (Biederman et al., 2007b), adolescents (Findling et al., 2011), and adults (Adler et al., 2008). Studies in a laboratory school setting and in a simulated adult workplace environment have demonstrated that the therapeutic benefits of LDX are ongoing at 13 h post-dose in children (Wigal et al., 2009) and 14 h post-dose in adults (Wigal et al., 2010). The present European, phase 3 trial evaluated the efficacy and safety of LDX over the course of 7 weeks in children and adolescents (6–17 years old) diagnosed with ADHD of at least moderate severity. Osmotic-release oral system methylphenidate (OROS-MPH) was included as a reference arm.

2. Experimental procedures

This randomized, double-blind, parallel-group, dose-optimized, placebo-controlled study (ClinicalTrials.gov Identifier: NCT00763971) was conducted in accordance with the current applicable regulations, the International Conference on Harmonisation of Good Clinical Practice, and local ethical and legal requirements. The study protocol was approved by an independent ethics committee/institutional review board and regulatory agency in each center (as appropriate) before study initiation. Each patient's parent or legal guardian provided written, informed consent, and assent was obtained from each participant, as applicable, before commencing study-related procedures.

2.1. Study population

The study enrolled male and female children (6–12 years old) and adolescents (13–17 years old) who satisfied the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) criteria for a primary diagnosis of ADHD (American Psychiatric Association, 2000). Patients had ADHD of at least moderate severity, as defined by a baseline ADHD Rating Scale version IV (ADHD-RS-IV) total score of 28 or higher. Additional inclusion criteria included: age-appropriate intellectual functioning; blood pressure measurements within the 95th percentile for age, sex, and height; and ability to swallow a capsule. Girls of childbearing potential had to have a negative urine pregnancy test at baseline and to comply with any contraceptive requirements of the protocol.

Key exclusion criteria included: failure to respond to previous OROS-MPH therapy; presence of a comorbid psychiatric diagnosis with significant symptoms (based on Kiddie-Schedule for Affective Disorders and Schizophrenia for school age children – Present and Lifetime – diagnostic interview); conduct disorder (excluding oppositional defiant disorder); pregnancy or lactation; weight below 22.7 kg; body mass index (BMI, kg/m^2) greater than the 97th percentile for age and sex; positive urine drug test (with the exception of the patient's current ADHD therapy); clinically significant electrocardiogram or laboratory abnormalities; suspected substance abuse or dependence disorder (excluding nicotine) within the previous 6 months; history of seizures; tics or Tourette's disorder; known structural cardiac abnormality; or any other condition that might increase vulnerability to the sympathomimetic effects of a stimulant drug. Patients whose current ADHD medication provided effective control of symptoms with acceptable tolerability were also excluded.

2.2. Study drug administration

Eligible patients completed a screening and washout period (3–42 days) and were randomized in a 1:1:1 ratio at baseline (visit 0) to receive once-daily LDX, OROS-MPH, or placebo for a 7-week double-blind evaluation period (4-week stepwise dose-optimization period

[visits 1–4] and 3-week dose-maintenance period [visits 5–7]), followed by an immediate 1-week washout and safety follow-up (visit 8). LDX was administered as 30, 50, or 70 mg capsules and OROS-MPH as 18, 36, or 54 mg tablets (54 mg/day is the maximum approved dose of OROS-MPH in Europe). An interactive voice/web response system was used to allocate a unique randomization number to each patient. Study drugs were over-encapsulated and appeared identical. Randomization was stratified by country and age group (6–12 or 13–17 years old). Enrollment was managed so that adolescents comprised approximately 25% of the study population.

Dosing began in the morning (approximately 07:00) after completion of the baseline visit. Patients initially received LDX 30 mg/day, OROS-MPH 18 mg/day, or placebo. If an acceptable response was not achieved, dose adjustments were made in a stepwise manner at weekly intervals to higher doses. An acceptable response was defined as at least a 30% reduction in ADHD-RS-IV total score from baseline and a Clinical Global Impressions-Improvement (CGI-I) rating of 1 (very much improved) or 2 (much improved), with tolerable adverse effects. A reduction of one dose level was permitted if individuals experienced an intolerable adverse effect. Doses could not be modified after visit 3; patients unable to tolerate the study drug were withdrawn from the study. Participants who achieved an acceptable response were maintained on their optimal dose for the remainder of the double-blind evaluation period (visits 4–7). Weekly on-site visits were scheduled for assessments of safety and efficacy, with reference to baseline.

2.3. Efficacy

The primary efficacy measure was the change from baseline in the investigator-rated ADHD-RS-IV total score at endpoint. Endpoint was defined as the last on-therapy, post-randomization treatment visit at which a valid ADHD-RS-IV total score was observed. The ADHD-RS-IV consists of 18 items designed to reflect current symptomatology of ADHD, based on DSM-IV-TR criteria. Each item is scored on a 4-point scale, ranging from 0 (no symptoms) to 3 (severe symptoms), with the total score ranging from 0 to 54. The scale is divided into two subscales (hyperactivity/impulsivity and inattention) of nine items each. A decrease from baseline in ADHD-RS-IV score indicated improvement in ADHD symptoms.

The key secondary efficacy measure was the CGI-I rating. The CGI-I is a 7-point global measure of clinical and functional improvement ranging from 1 (very much improved) to 7 (very much worse). At baseline, the CGI-Severity (CGI-S) rating was used to measure the severity of each patient's condition on a 7-point scale, ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill). At each subsequent visit, the investigator assessed the individual's improvement relative to baseline using the CGI-I rating; results were categorized as 'improved' (all patients regarded as 'very much improved' or 'much improved' [i.e. CGI-I of 1 or 2]) or 'not improved' (all other scores).

2.4. Safety

Safety assessments included treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, physical examinations, vital signs, and electrocardiograms. TEAEs were defined as adverse events that started or worsened during the period between the first dose of study drug and the third day (inclusive) following cessation of treatment. TEAEs were coded using the current version of the *Medical Dictionary for Regulatory Activities* (version 11.1) and summarized by system organ class, preferred term, and treatment group for the number and proportion reporting the event. TEAE intensity was classified as mild (easily tolerated and does not interfere with usual activity), moderate (interferes with usual activity, but patient is still able to function), or severe (incapacitating and patient is unable to work or complete usual activity).

2.5. Statistical analyses

Safety outcomes were assessed for the safety population, defined as all patients who took at least one dose of study drug. Efficacy outcomes were assessed for the full analysis set, defined as all patients who were randomized and took at least one dose of study drug, but excluding patients (n=15) from one site owing to violations of Good Clinical Practice. A last observation carried forward approach (excluding baseline) was used when efficacy assessments were incomplete for a patient owing to early withdrawal from the study or missing data.

The changes from baseline in the ADHD-RS-IV total and subscales scores at each study visit and endpoint were analyzed using an analysis of covariance (ANCOVA) model. Least squares (LS) mean and p values were based on type III sum of squares from the ANCOVA model for the change from baseline, including treatment group (effect of interest), country and age group (randomization blocking factors), and the corresponding baseline score (covariate). The primary treatment comparison (LDX versus placebo) was evaluated at a significance level of 0.05 (two-sided). The null hypothesis stated that there was no difference between LDX and placebo at endpoint, with the two-sided alternative of a non-zero difference between groups. The Cochran–Mantel–Haenszel test stratified by country and age group was used to assess the key secondary efficacy measure (CGI-I), and compared the proportions of patients in each treatment group who were 'improved' and 'not improved' at each study visit and at endpoint. The statistical analysis plan for the study did not prespecify a formal statistical comparison between LDX and OROS-MPH.

Effect sizes based on the changes in ADHD-RS-IV total and subscale scores were calculated as the difference (active drug−placebo) in LS mean score, divided by the root mean square error obtained from the ANCOVA model. Effect sizes of 0.2, 0.5, and 0.8 are traditionally held to correspond to small, medium, and large magnitudes of effect, respectively (Cohen, 1992). To detect an effect size of at least 0.45 for LDX compared with placebo, with power of 90% and significance level of 0.05 (two-sided) using a two-sample t-test with equal allocation to treatment groups, 111 randomized patients were required for each treatment group. A further 111 participants were randomized to an OROS-MPH group to provide reference data for an approved comparator product. Therefore, inclusion of a total of 333 randomized patients was planned.

3. Results

3.1. Patient disposition and baseline characteristics

The study was conducted between 17 November 2008 and 16 March 2011 at 48 centers in 10 European countries (Germany, Sweden, Spain, Hungary, France, the UK, Italy, Belgium, Poland, and the Netherlands). Of 336 randomized patients, 196 (58.3%) completed the study (Figure 1). The most frequently reported reason for study discontinuation was the lack of efficacy, which occurred in 11/113 (9.7%), 54/111 (48.6%), and 22/112 (19.6%) patients treated with LDX, placebo, and OROS-MPH, respectively (Figure 1). Baseline characteristics were similar across treatment groups (Table 1). The mean age ($\pm$ standard deviation [SD]) across treatment groups was 10.9$\pm$2.8 years; children and adolescents comprised 71.1% and 28.9% of patients, respectively (safety population).

3.2. Dose optimization

Following dose optimization, 20/111 (18.0%) patients in the LDX treatment group received an optimal dose of 30 mg/day

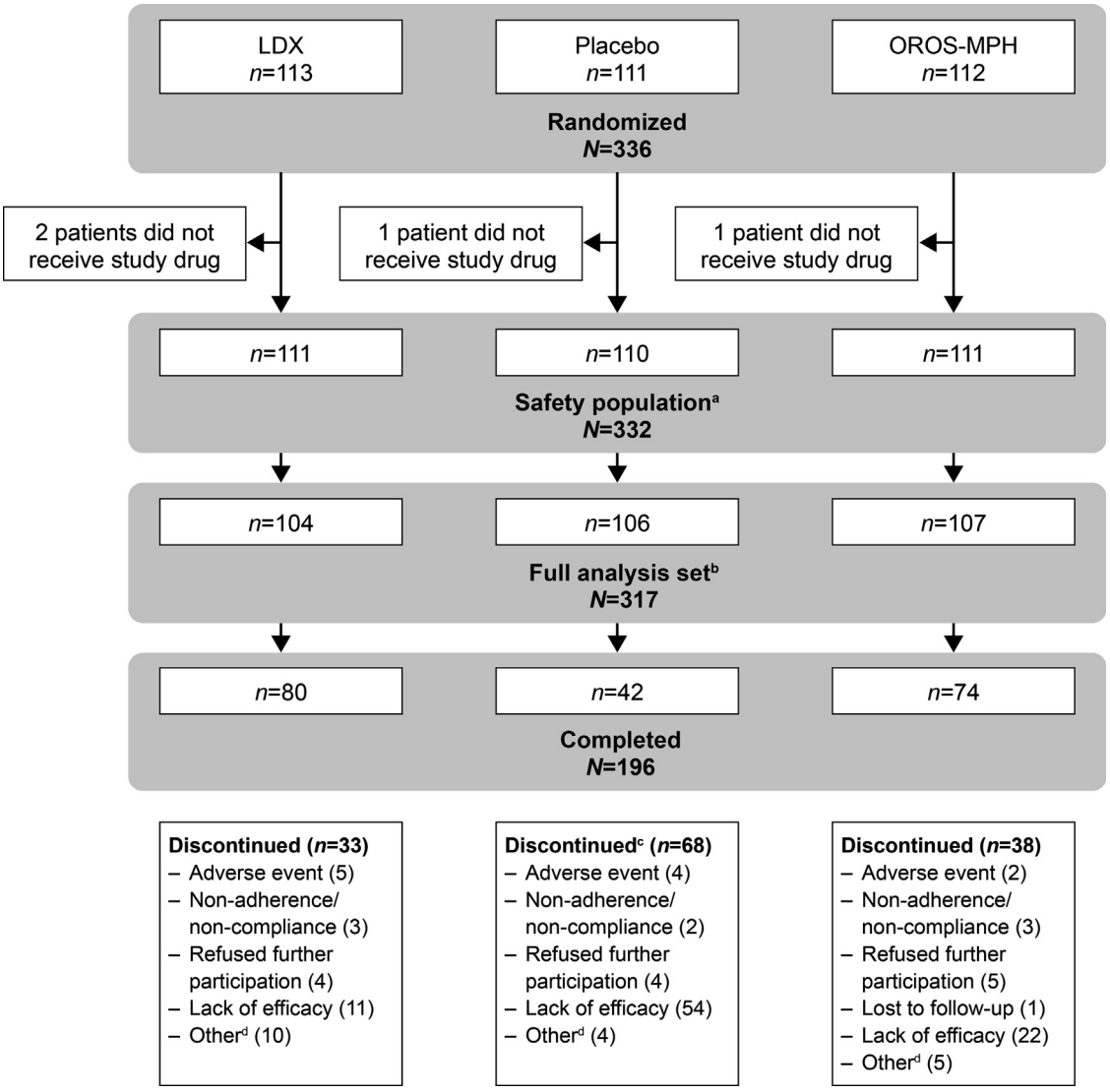

Figure 1 Patient disposition. [a]Safety population included all patients who took one dose of any study drug. [b]Full analysis set included all patients who were randomized and took at least one dose of study drug; patients from one site ($n=15$) were excluded from the full analysis set owing to violations of Good Clinical Practice. [c]One patient (placebo group) had a missing end-of-study page, so the number of completers plus number of early terminators is one less than the number randomized. [d]Other reasons for study discontinuation included: unable to swallow capsule, personal reasons due to family, and medical monitor decision.

during the dose-maintenance period, 33/111 (29.7%) patients received 50 mg/day, and 37/111 (33.3%) patients received 70 mg/day (safety population). In the OROS-MPH treatment group, 11/111 (9.9%) patients were optimized to 18 mg/day, 22/111 (19.8%) patients to 36 mg/day, and 59/111 (53.2%) patients to 54 mg/day (safety population). The mean ($\pm$ SD) optimal dose was 53.8 ± 15.6 mg/day for LDX and 45.4 ± 12.7 mg/day for OROS-MPH (safety population).

3.3. Efficacy

ADHD-RS-IV total scores at baseline were similar across treatment groups (Table 1). Mean ($\pm$ SD) ADHD-RS-IV total scores at baseline and endpoint for each treatment group are shown in Figure 2. The LS mean ($\pm$ standard error [SE]) changes in ADHD-RS-IV total score from baseline to endpoint were greater for LDX (-24.3 ± 1.2) and OROS-MPH (-18.7 ± 1.1) than for placebo (-5.7 ± 1.1) (Figure 2). The difference in LS mean change (95% confidence interval [CI]) in ADHD-RS-IV total score between LDX and placebo was statistically significant in favor of LDX at study endpoint (-18.6 [-21.5 to -15.7], $p<0.001$) and at every on-treatment visit ($p<0.001$ for all visits) (Figure 3). The difference in LS mean change (95% CI) in ADHD-RS-IV total score between OROS-MPH and placebo was statistically significant in favor of OROS-MPH at study endpoint (-13.0 [-15.9 to -10.2], $p<0.001$) and at every on-treatment visit ($p<0.01$ at visit 1, $p<0.001$ thereafter). Effect sizes based on the difference (active drug $-$ placebo) in LS mean change in ADHD-RS-IV total score from baseline to endpoint were 1.80 and 1.26 for LDX and OROS-MPH, respectively.

The decreases in both the ADHD-RS-IV hyperactivity/impulsivity and inattention subscale scores from baseline

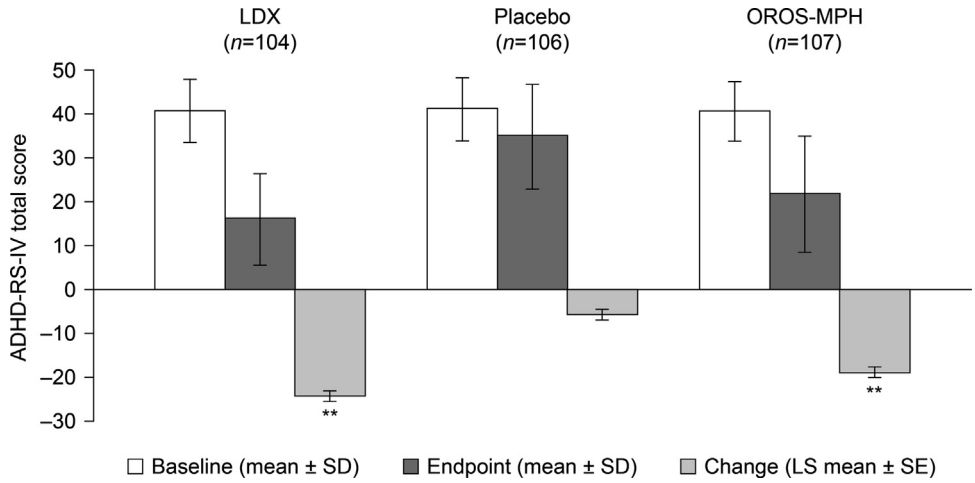

Figure 2 ADHD-RS-IV mean total scores at baseline and endpoint (±SD), and LS mean changes (±SE) from baseline to endpoint (full analysis set). $^{**}p<0.001$ based on difference in LS mean change (active drug−placebo). Endpoint is the last on-treatment, post-baseline visit of the dose-optimization or dose-maintenance period (visits 1–7) with a valid ADHD-RS-IV total score. A decrease from baseline in the ADHD-RS-IV total score indicates an improvement in ADHD symptomatology.

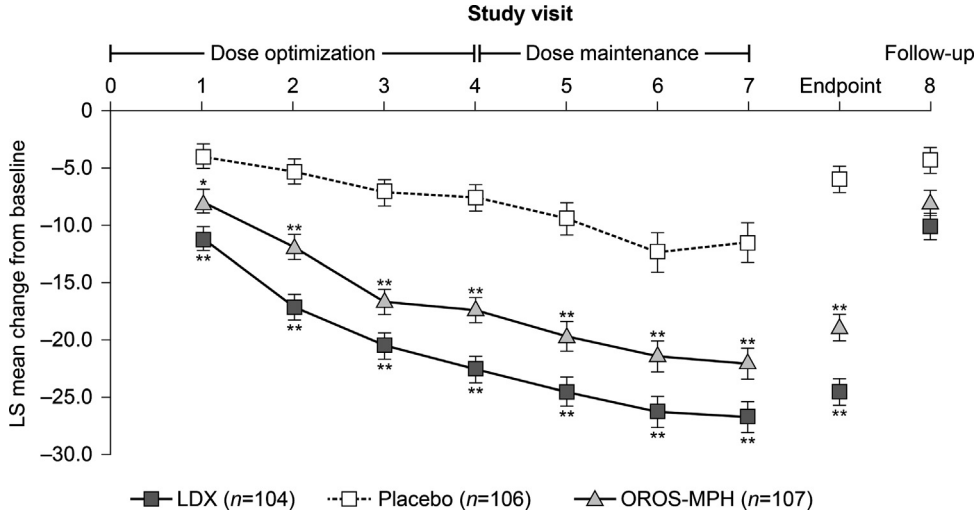

Figure 3 LS mean changes (±SE) in ADHD-RS-IV mean total scores from baseline at each study visit (full analysis set). $^{*}p<0.01$, $^{**}p<0.001$ based on difference in LS mean change (active drug - placebo). Endpoint is the last on-treatment, post-baseline visit of the dose-optimization or dose-maintenance period (visits 1–7) with a valid ADHD-RS-IV total score. Visit 7 was the last day of treatment and the interval between visits 7 and 8 was a 1-week post-treatment washout period. A decrease from baseline in the ADHD-RS-IV total score indicates an improvement in ADHD symptomatology.

to endpoint were also significantly greater for both LDX and OROS-MPH than for placebo (Figure 4). The differences in LS mean change (95% CI) from baseline to endpoint between LDX and placebo were statistically significant for the hyperactivity/impulsivity (−8.7 [−10.3 to −7.2], $p<0.001$; effect size, 1.60) and inattention (−9.9 [−11.5 to −8.3], $p<0.001$; effect size, 1.72) subscale scores. The differences between OROS-MPH and placebo in LS mean (95% CI) change from baseline to endpoint were significant for the hyperactivity/impulsivity (−6.0 [−7.5 to −4.5], $p<0.001$; effect size, 1.11) and inattention (−7.0 [−8.6 to −5.4], $p<0.001$; effect size, 1.22) subscale scores.

The proportions (95% CI) of patients with a CGI-I rating of 1 ('very much improved') or 2 ('much improved') at endpoint were 78% (70–86), 14% (8–21), and 61% (51–70) for LDX, placebo, and OROS-MPH, respectively (Figure 5). The difference between LDX and placebo in the proportion of individuals categorized as 'improved' was statistically significant at visits 1–7 and at endpoint ($p<0.001$, Figure 5). The difference between OROS-MPH and placebo for the proportion of patients with a CGI-I rating of 1 or 2 was statistically significant at visits 2–7 and at endpoint ($p<0.001$, Figure 5).

3.4. Safety

TEAEs were experienced by 80/111 (72.1%), 63/110 (57.3%), and 72/111 (64.9%) patients receiving LDX, placebo, and OROS-MPH, respectively (Table 2). TEAEs with a frequency of at least 5% in those receiving LDX included decreased appetite, headache, insomnia, decreased weight, nausea, and anorexia (Table 2). Most TEAEs were mild or moderate

in intensity (Table 2). The proportions of patients who reported serious TEAEs were low across all treatment groups (Table 2). The serious TEAEs were considered by the investigators not to be related to the study drug, with one exception in the OROS-MPH group (overdose). No deaths were reported in this study and few patients experienced a TEAE leading to discontinuation of study drug (Table 2). TEAEs leading to discontinuation of study drug in the LDX group were vomiting, anorexia, decreased appetite, angina pectoris, tachycardia, decreased weight, and insomnia. The case of angina pectoris was a 13-year old boy who experienced pre-cardiac pain, which was considered by the study investigator to be of moderate intensity and did not meet the criteria for a serious TEAE. During the study, this patient had no clinically significant laboratory abnormalities, no treatment or concomitant medications were reported and all electrocardiograms were normal. Decreased appetite, irritability, and insomnia were the TEAEs that led to discontinuation of study drug in the OROS-MPH group.

LDX and OROS-MPH were associated with modest increases in mean pulse rate, heart rate, systolic blood pressure, and diastolic blood pressure, and decreases in mean body weight from baseline to endpoint (Table 3). Of 47 patients (LDX, $n=35$; OROS-MPH, $n=12$) who had a potentially clinically significant decrease in weight at endpoint ($\geq$7% from baseline), three patients (LDX, $n=2$; OROS-MPH, $n=1$) moved from healthy weight BMI categories to underweight (defined as BMI less than the 5th percentile).

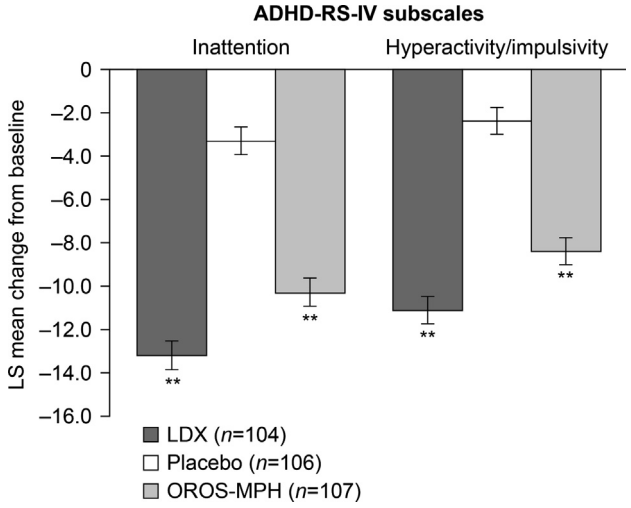

Figure 4 LS mean change ($\pm$SE) from baseline to endpoint for ADHD-RS-IV inattention and hyperactivity/impulsivity subscale scores (full analysis set). $^{**}p<0.001$ based on difference in LS mean change (active drug−placebo). Endpoint is the last on-treatment, post-baseline visit of the dose-optimization or dose-maintenance period (visits 1–7) with a valid ADHD-RS-IV total score. A decrease from baseline in the ADHD-RS-IV subscale score indicates an improvement in ADHD symptomatology.

4. Discussion

In this European, 7-week, phase 3 study, LDX was more effective than placebo in improving symptoms in children and adolescents with ADHD. Compared with placebo, significant improvements in both ADHD core symptoms and global functioning were observed. LDX was well tolerated, with TEAEs consistent with those reported in previous studies. Robust efficacy outcomes were also observed for OROS-MPH, which was included in this study as a reference arm.

The primary outcome measure was the change from baseline in ADHD-RS-IV total score. Mean ADHD-RS-IV total scores at baseline were indicative of moderate-to-marked symptoms before administration of study drug (Goodman et al., 2010). LDX produced a decrease in ADHD-RS-IV total score from baseline that was significantly greater than placebo by the first on-treatment study visit, scheduled 1 week following treatment initiation. At endpoint, the mean ADHD-RS-IV total score in patients treated with LDX was reduced by more than 50% compared with baseline. A 50% reduction in ADHD-RS-IV

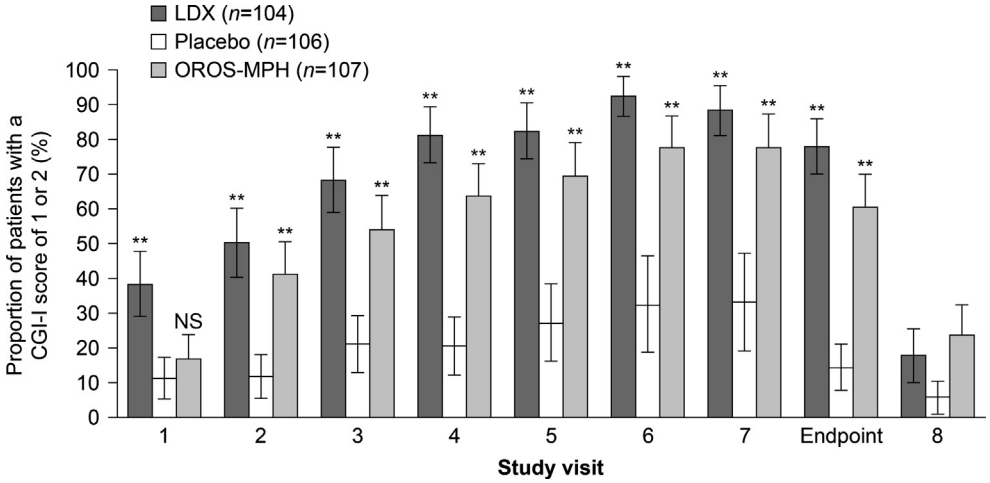

Figure 5 Proportion of patients with a CGI-I rating of 1 ('very much improved') or 2 ('much improved') ($\pm$95% CI) at each study visit compared with baseline (full analysis set). $^{*}p<0.01$, $^{**}p<0.001$ versus placebo (based on Cochran-Mantel-Haenszel test stratified by country and age group). Percentages are based on the number of patients with data at that visit in each treatment group. Endpoint is the last on-treatment, post-baseline visit of the dose-optimization or dose-maintenance period (visits 1–7) with a valid CGI-I assessment. The interval between visits 7 and 8 was a 1-week post-treatment washout period.

Table 1 Baseline characteristics and demographic data according to treatment group (safety population).

Characteristic	LDX (*n*=111)	Placebo (*n*=110)	OROS-MPH (*n*=111)
Age (years)			
Mean (SD)	10.9 (2.9)	11.0 (2.8)	10.9 (2.6)
Median (range)	11.0 (6-17)	11.0 (6-17)	11.0 (6-16)
Age distribution (years), *n* (%)			
6-12	77 (69.4)	79 (71.8)	80 (72.1)
13-17	34 (30.6)	31 (28.2)	31 (27.9)
Male, *n* (%)	87 (78.4)	91 (82.7)	90 (81.1)
Ethnicity, *n* (%)			
Hispanic or Latino	2 (1.8)	0	2 (1.8)
Not Hispanic or Latino	109 (98.2)	110 (100.0)	109 (98.2)
Race, *n* (%)			
White	107 (96.4)	108 (98.2)	107 (96.4)
Black or African American	1 (0.9)	0	0
Asian	1 (0.9)	0	0
Other	2 (1.8)	2 (1.8)	4 (3.6)
Body mass index (kg/m^2)			
Mean (SD)	19.3 (3.7)	19.0 (3.3)	19.1 (3.2)
Median (range)	18.6 (13.9-29.7)	18.0 (13.9-27.3)	18.6 (14.3-29.8)
ADHD-RS-IV total score at baseline[a]			
Mean (SD)	41.0 (7.3)	41.2 (7.2)	40.4 (6.8)
Median (range)	41.0 (28-54)	42.0 (28-54)	40.0 (28-54)
ADHD-RS-IV hyperactivity/impulsivity subscale score at baseline[a]			
Mean (SD)	18.5 (6.2)	19.3 (5.1)	18.5 (5.5)
Median (range)	20.0 (1-27)	20.0 (8-27)	19.0 (1-27)
ADHD-RS-IV inattention subscale score at baseline[a]			
Mean (SD)	22.6 (3.4)	21.9 (3.7)	21.9 (3.5)
Median (range)	23.0 (13-27)	22.0 (10-27)	22.0 (14-27)
CGI-S rating at baseline[a]			
Mean (SD)	5.0 (0.8)	4.9 (0.8)	5.0 (0.8)
Median (range)	5.0 (4-7)	5.0 (3-7)	5.0 (3-7)
ADHD subtype[b], *n* (%)			
Predominantly inattentive	23 (20.7)	16 (14.5)	14 (12.7)
Predominantly hyperactive-impulsive	2 (1.8)	7 (6.4)	1 (0.9)
Combined	86 (77.5)	87 (79.1)	95 (86.4)
Time since ADHD diagnosis (years)[b]			
Mean (SD)	2.4 (2.9)	2.2 (2.6)	2.2 (2.5)
Median (range)	1.3 (0.0-10.9)	0.90 (0.0-10.2)	0.8 (0.0-9.0)
Concomitant psychiatric diagnosis, *n* (%)[c]			
Any	19 (17.1)	20 (18.2)	29 (26.1)
Oppositional defiant disorder	8 (7.2)	8 (7.3)	10 (9.0)
Previously treated with any ADHD medication, *n* (%)	64 (57.7)	58 (52.7)	60 (54.1)

[a]Five patients had no baseline ADHD-RS-IV total score, ADHD-RS-IV hyperactivity/impulsivity subscale score, ADHD-RS-IV inattention subscale score and CGI-S rating.

[b]One patient in the OROS-MPH group was not evaluated for ADHD subtype or time since ADHD diagnosis. Percentages are based on the number of patients in each treatment group.

[c]Patients with at least one ongoing definite psychiatric diagnosis based on the Kiddie-Schedule for Affective Disorders and Schizophrenia for school age children – Present and Lifetime – diagnostic interview.

Table 2 Summary of TEAEs according to treatment group (safety population).

TEAE—preferred term, *n* (%)	LDX (*n*=111)	Placebo (*n*=110)	OROS-MPH (*n*=111)
Any TEAE	80 (72.1)	63 (57.3)	72 (64.9)
Mild	33 (29.7)	35 (31.8)	30 (27.0)
Moderate	40 (36.0)	25 (22.7)	40 (36.0)
Severe	7 (6.3)	3 (2.7)	2 (1.8)
Any serious TEAE[a]	3 (2.7)	3 (2.7)	2 (1.8)
Any TEAE leading to discontinuation of study drug	5 (4.5)	4 (3.6)	2 (1.8)
TEAEs (≥5% of patients in any treatment group)[b]			
Decreased appetite	28 (25.2)	3 (2.7)	17 (15.3)
Headache	16 (14.4)	22 (20.0)	22 (19.8)
Insomnia	16 (14.4)	0	9 (8.1)
Decreased weight	15 (13.5)	0	5 (4.5)
Nausea	12 (10.8)	3 (2.7)	8 (7.2)
Anorexia	12 (10.8)	2 (1.8)	6 (5.4)
Nasopharyngitis	8 (7.2)	8 (7.3)	14 (12.6)
Upper abdominal pain	8 (7.2)	6 (5.5)	9 (8.1)
Abdominal pain	6 (5.4)	6 (5.5)	4 (3.6)
Sleep disorder	6 (5.4)	1 (0.9)	2 (1.8)
Cough	3 (2.7)	0	8 (7.2)
Initial insomnia	3 (2.7)	1 (0.9)	7 (6.3)

[a]Serious TEAEs were syncope, gastroesophageal reflux disease, appendicitis (LDX); loss of consciousness, hematoma, clavicle fracture (placebo); overdose, syncope (OROS-MPH).
[b]TEAEs are presented in order of decreasing frequency in the LDX treatment group.

Table 3 Summary of vital signs, weight, and electrocardiogram parameters (safety population).

	LDX (*n*=111)	Placebo (*n*=110)	OROS-MPH (*n*=111)
Systolic blood pressure (mmHg)			
Baseline, mean (SD)	107.4 (10.4)	107.8 (10.4)	107.1 (9.9)
Endpoint, mean change (SD)	+1.0 (9.8)	+1.0 (9.6)	+0.3 (11.1)
Diastolic blood pressure (mmHg)			
Baseline, mean (SD)	68.3 (9.9)	66.1 (9.1)	65.0 (9.5)
Endpoint, mean change (SD)	+0.2 (9.6)	+1.2 (8.7)	+1.7 (9.9)
Pulse (bpm)			
Baseline, mean (SD)	75.0 (11.7)	77.5 (11.5)	76.6 (10.2)
Endpoint, mean change (SD)	+5.5 (13.2)	−0.6 (10.6)	+3.4 (13.2)
Weight (kg)			
Baseline, mean (SD)	45.0 (17.5)	43.1 (14.0)	43.6 (15.1)
Endpoint, mean change (SD)	−2.1 (1.9)	+0.7 (1.0)	−1.3 (1.4)
Heart rate (bpm)			
Baseline, mean (SD)	74.6 (12.1)	77.2 (10.3)	75.9 (10.2)
Endpoint, mean change (SD)	+5.7 (15.3)	−1.1 (9.6)	+5.0 (12.8)
QTcF interval (ms)			
Baseline, mean (SD)	376.9 (16.4)	377.9 (17.4)	375.9 (16.4)
Endpoint, mean change (SD)	+0.3 (15.6)	+2.0 (13.6)	+0.2 (15.9)

bpm, beats per minute; QTcF, QT interval corrected using Fridericia's formula.

total score has been proposed to be more clinically-meaningful than the 25% or 30% reduction thresholds that are often used to define a response in clinical trials (Goodman et al., 2010). Similar treatment benefits were observed for both the hyperactivity/impulsivity and inattention subscales of the ADHD-RS-IV.

The large effect size obtained for LDX (1.80) is similar to those obtained previously in a fixed-dose study conducted in North America (range, 1.21–1.60) (Biederman et al., 2007b) and indicates robust treatment efficacy (Cohen, 1992). Although several factors can influence effect sizes (Faraone, 2012), preliminary investigations have suggested that the small SD values obtained for the change in ADHD-RS-IV score in the LDX and placebo groups do not account for the large magnitude of the effect size. It is, however, possible that the smaller than usual placebo response did, at least in part, contribute to this large treatment effect. ADHD is currently less frequently diagnosed in Europe than in North America, with evidence of under-recognition and under-diagnosis (NHS Quality Improvement Scotland, 2008). Consequently, it is likely that those individuals who are diagnosed are at the more severe end of the spectrum and would therefore be less likely to show a response to placebo. In agreement with this suggestion, reassessment of data from the Multimodal Treatment of ADHD (MTA) study demonstrated that children who had been diagnosed with ADHD based on DSM-IV criteria, but also met the more restrictive International Classification of Diseases-10 criteria for hyperkinetic disorder, showed a more robust response to medication compared with those who met DSM-IV criteria alone (Santosh et al., 2005).

In addition to reducing the core symptoms of ADHD, this trial has also demonstrated that LDX improved global functioning, as assessed using the CGI-I rating. The proportion of patients with an improved CGI-I rating was higher in the LDX group than in the placebo group at every on-treatment study visit, with 78% of participants reportedly 'very much improved' or 'much improved' (CGI-I score of 1 or 2) at study endpoint compared with 14% of patients in the placebo group.

This study was not designed to provide a head-to-head comparison between LDX and OROS-MPH. However, the results observed for the OROS-MPH reference arm support the validity and sensitivity of the study design and execution. OROS-MPH treatment produced a significantly greater improvement in ADHD-RS-IV total score than placebo, with a large effect size of 1.26. Furthermore, a significantly greater proportion of patients taking OROS-MPH had a CGI-I rating of 1 or 2 from the second on-treatment study visit (visit 2) compared with those who received placebo.

LDX and OROS-MPH were generally well tolerated in this study, and most TEAEs were mild or moderate in severity. The safety profile of LDX was consistent with that reported in previous studies (Adler et al., 2008; Biederman et al., 2007a, 2007b; Findling et al., 2011) and with the known effects of stimulant medications (May and Kratochvil, 2010). Anorexia, decreased appetite, decreased weight, insomnia, and nausea were more common in patients treated with LDX than in those who received OROS-MPH, whereas headache was reported more frequently in the OROS-MPH treatment group than in the LDX treatment group. Most participants receiving LDX and OROS-MPH completed the study. In the LDX treatment group, TEAEs that led to discontinuation of study drug included anorexia, decreased appetite and vomiting. In the OROS-MPH group, one participant discontinued owing to decreased appetite; none discontinued due to vomiting.

The modest mean increases from baseline in heart rate and pulse rate in patients receiving LDX and OROS-MPH are consistent with the known safety profiles of stimulant medications (May and Kratochvil, 2010). The decrease in mean weight that was observed in the LDX treatment group was greater than that observed in the OROS-MPH group. However, at endpoint, most patients remained within their baseline BMI category and few participants had weight changes that resulted in a shift to the underweight BMI category. The clinical significance of the observed weight loss in patients treated with LDX is unclear, given the short-term nature of the trial. An open-label investigation into the long-term (up to 12 months) efficacy and safety of LDX in school-aged children found that weight increased in patients taking LDX over the course of the study (Findling et al., 2008). However, the rate of this increase was below the age- and sex-norm, suggesting that weight should be monitored during extended LDX treatment. The long-term efficacy and safety of LDX is being investigated in an extension to the present study, which includes an open label phase followed by a randomized, double-blind, withdrawal phase.

The strengths of this study include its randomized, double-blind, placebo-controlled design, the large number of patients enrolled at multiple centers across Europe, and the inclusion both of children and of adolescents. However, there are some limitations that should be taken into consideration when interpreting the results. Firstly, individuals with comorbid conditions, such as post-traumatic stress disorder, bipolar affective disorder, or severe anxiety disorder, were excluded from this study. Secondly, due to European regulations, the maximum dose of OROS-MPH that was administered in this study was 54 mg/day. In the US, 72 mg/day OROS-MPH has been approved for the treatment of patients with ADHD who are at least 13 years old (American Academy of Pediatrics, 2011a). Nevertheless, a robust effect size (1.26) based on the change in ADHD-RS-IV total score from baseline to endpoint was obtained for patients treated with OROS-MPH. Finally, compared with a fixed-dose methodology, the 3-week dose-optimization period was designed to reflect more closely the common prescribing practices of clinicians treating patients with ADHD. The optimized-dose design of the study did, however, preclude evaluation of the dose-dependency of either efficacy or safety outcomes, as well as confirmation of dose equivalence between LDX and OROS-MPH.

This phase 3 study was the first in Europe to evaluate the efficacy and safety of a once-daily optimized dose of LDX in children and adolescents with at least moderately symptomatic ADHD. LDX was more effective than placebo in improving core symptoms and global functioning in patients with ADHD, and demonstrated a safety profile consistent with the results from previous studies and with long-acting stimulant use.

Role of the funding source

This study was supported by funding from Shire Development LLC.

Contributors

T Banaschewski, D Coghill, M Johnson, M Lecendreux, C Soutullo, and A Zuddas were principal investigators in this clinical study.

C Anderson, R Civil, N Higgins, A Lyne, and L Squires contributed to the study design. A Lyne was responsible for the statistical analysis. All authors were involved in discussion and interpretation of the data and have critically revised the article and approved the manuscript before submission.

Conflict of interest

C Anderson, R Civil, N Higgins, A Lyne, and L Squires are employees of Shire and own stock/stock options. The following authors have received compensation for serving as consultants or speakers, or they or the institutions they work for have received research support or royalties from the companies or organizations indicated: D Coghill (Flynn, Janssen Cilag, Lilly, Medice, Novartis, Otsuka, Oxford University Press, Pfizer, Schering-Plough, Shire, UCB, Vifor Pharma); T Banaschewski (Bristol-Myers Squibb, Desitin, Develco Pharma, Janssen McNeil, Lilly, Medice, Novartis, Shire, UCB, Vifor Pharma); M Lecendreux (Shire, UCB, Vifor Pharma); C Soutullo (Abbott, Alicia Koplowitz Foundation, AstraZeneca, Bristol-Myers Squibb, Carlos III Institute [FIS]: Redes Temáticas de Investigación Cooperativa, DOYMA, Editorial Médica Panamericana, Eli Lilly, EUNSA, European Interdisciplinary Network ADHD Quality Assurance, Euro RSCG Life Medea, GlaxoSmithKline, Gobierno de Navarra, Grupo Aula Médica, Grupo Correo, Janssen, Medice/Juste, Novartis, Otsuka, Pfizer, University of Navarra Research Projects (PIUNA), SEP-SEPB, Shire, Sociedad Vasco-Navarra Psiquiatría, Solvay, Stanley Medical Research Institute-National Alliance on Mental Illness, Wolters Kluwer); M Johnson (Janssen, Lilly, Novartis, Shire, Vifor Pharma, WM Lundgrens Research Fund); A Zuddas (AstraZeneca, Bristol-Myers Squibb/Otsuka, Lilly, Lundbeck, Shire, Vifor Pharma).

Acknowledgments

The authors thank the patients and the investigators who took part in this study, and Dr. Eric Southam and Dr. Elizabeth Gandhi of Oxford PharmaGenesis™ Ltd. for editorial assistance, collating the comments of the authors, and editing the manuscript for submission.

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